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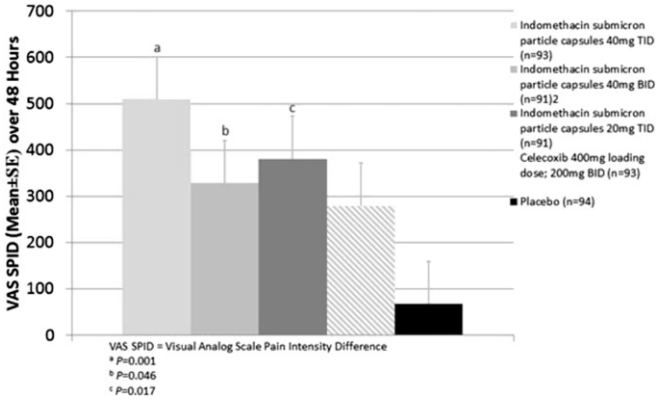
bunionectomy with osteotomy and fixation under regional anesthesia. Patients with a pain intensity rating of ≥40mm on a 100mm Visual Analog Scale (VAS) were randomized to receive indomethacin submicron particle capsules (40mg TID or BID or 20mg TID), celecoxib (400mg loading dose; 200mg BID), or placebo. The primary endpoint was the summed pain intensity difference measured by VAS over 48 hrs (VAS SPID-48).

Results: Of the 462 patients enrolled, most (83.1%) were women with a mean age of 41.2 (±12.5) years. Indomethacin submicron particle capsules 40mg TID (509.6±91.9), 40mg BID (328.0±92.9), and 20mg TID (380.5±92.9) reduced pain (VAS SPID-48; $P \leq 0.046$ for all 3 groups) compared with placebo (67.8±91.4; Figure). Although there was some evidence of analgesia for celecoxib (279.4±91.9) VAS SPID-48 did not achieve statistical significance compared with placebo. Indomethacin submicron particle capsules 40mg TID (30.7; $P=0.013$) and 40mg BID (29.8; $P=0.014$) achieved better pain control over 4 hrs after study entry (VAS SPID-4) compared to placebo (8.9). Similarly, indomethacin submicron particle capsules 40mg TID (2.5; $P=0.003$) and 40mg BID (2.1; $P=0.022$) provided greater total pain relief over 4 hrs after study entry (TOTPAR-4) compared with placebo (1.2). Some evidence of pain control was observed as early as 30 min (VAS SPID) in the indomethacin submicron particle capsules 40mg TID (2.9) and 40mg BID (2.6) groups compared with placebo (0.2). AEs were generally similar across treatment groups and included nausea, localized post-procedural edema, dizziness, and headache.



Conclusions: In this study, investigational lower-dose, indomethacin submicron particle capsules provided effective pain control compared with placebo in a post-surgical model of moderate to severe acute pain. Indomethacin submicron particle capsules are a potentially promising option for patients with acute pain.

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ACUTE AND SHORT-TERM EFFECTS OF INTRA-ARTICULAR KNEE PAIN RELIEF ON PAIN SENSITIZATION IN KNEE OA: A COHORT STUDY

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Purpose: Pain is the cardinal symptom of knee osteoarthritis (OA). Recently hyperalgesia and widespread pain was shown in knee OA patients, as both the knee and surrounding sites were hypersensitive to pressure pain testing compared with controls. Hyperalgesia and spontaneous pain in knee OA is most likely related to increased sensitivity of nociceptors located in deep tissue (peripheral sensitisation) and/or by increased responses in dorsal horn or supraspinal neurons (central sensitisation). However, the effects of pain relief on pain sensitivity in knee OA are unknown. The purpose of this study was to assess the effects of intra-articular pain relief and anti-inflammation on pain sensitivity in the knee and surrounding tissues in knee OA patients.

Methods: Twenty-five consecutive knee OA patients with symptomatic knee OA according to the ACR criteria were included in this observational study, with tests of pressure pain thresholds (PPT) before and after treatment of the knee with intra-articular injection of 40 ml glucocorticoid (depomedrol 40 mg/ml) and 10 ml lidocaine (10%). The patients rated their current pain continuously on a visual analogue scale (VAS), with 0 indicating "no pain" and 10 defined "maximum pain". Hand-held, computer-controlled and cuff pressure algometers were used to assess PPT in the peripatellar region, on vastus lateralis, on tibialis anterior and the extensor carpi radialis longus muscles (control site). The PPTs were assessed on day -8 and day 0 before, immediately after the injection (day 0) and two weeks after the injection (day 14).

Results: The current knee pain was significantly lower (see table 1) after treatment, indicating clinical efficacy of the injection. We found reduced pain sensitivity (higher PPT levels) following intra-articular lidocaine (see table 1 and 2 at day 0 - post lidocaine) in both the knee and in the surrounding muscles, whereas the control assessment site was not affected by either treatments. There was a trend towards even greater reduction in pain sensitivity at day 14 after the intra-articular treatment (see table 1 and 2 at day 14 follow-up) in both the knee and in the surrounding muscles.

Conclusions: This study shows that intra-articular knee pain relief leads to reduced pain sensitivity in the knee and surrounding muscles as well. This effect may be more pronounced after a combination of anaesthetic action and reduction of inflammation. Deeper understanding of the underlying mechanisms may influence the choice of treatment in the future to avoid or prevent hypersensitivity in knee OA patients.

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THE REDUCTION OF PAIN BY CHONDROCYTES SECRETING TGF-β1 IN A RAT MONOSODIUM IODOACETATE (MIA)-INDUCED OSTEOARTHRITIS MODEL

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Table 1

Test day	Day -8		Day 0				Day 14		P for trend
	Test 1		Test 2		Post lidocaine		Follow-up(post steroid)		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Current knee pain, cm (0-10)	3.0	0.3	2.8	0.3	1.8	0.3	1.3	0.3	0.0001
Hand-held algometer, kPa									
Corpus Hoffa medial	558.1	23.8	582.1	23.8	659.6	23.8	689.3	24.2	0.0001
Corpus Hoffa lateral	611.2	25.3	656.5	25.3	689.8	25.3	722.9	25.8	0.0057
Lateral joint line	490.6	17.3	524.6	17.3	601.3	17.3	573.8	17.6	<.0001
Quadriceps tendon, lateral	507.6	23.5	527.9	23.6	636.8	23.6	560.9	23.9	<.0001
Quadriceps tendon, median	580.2	22.9	597.1	22.9	675.3	22.9	672.8	23.4	0.0011
Quadriceps tendon, medial	490.4	21.3	538.3	21.3	625.3	21.3	582.9	21.8	<.0001
Medial joint line	506.1	23.3	513.5	23.3	596.5	23.3	568.3	23.6	0.0006
Centre of patella	629.0	23.7	669.5	23.7	707.3	23.7	702.3	24.1	0.0341
Extensor carpi radialis (control point)	412.0	16.1	430.5	16.1	452.5	16.1	428.7	16.5	0.3013

Table 2

Test day	Day -8		Day 0				Day 14		P for trend
	Test 1		Test 2		Post lidocaine		Follow-up(post steroid)		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Computer-controlled algometer, kg									
Corpus Hoffa	2.4	0.1	2.4	0.1	2.8	0.1	3.2	0.1	<.0001
Vastus lateralis	2.4	0.1	2.5	0.1	2.9	0.1	3.0	0.1	<.0001
Tibialis anterior	2.8	0.1	2.6	0.1	2.8	0.1	3.1	0.1	0.0006
Cuff algometer, kPa									
Lower leg	15.6	0.4	15.4	0.4	16.0	0.4	15.9	0.4	0.0214

Purpose: TissueGene-C (TG-C) is a mixture of normal human chondrocytes (hChonJ) and genetically modified chondrocytes to express TGF-β1 (hChonJb#7), and currently undergoing phase 2 clinical trials for osteoarthritis. Phase 2a clinical trials have shown that TG-C treatment significantly reduced pain when administered to the osteoarthritic patients. In this study, we investigated the effect on pain reduction by the chondrocytes expressing TGF-β (hChonJb#7) which is a component of TG-C.
Methods: Monosodium iodoacetate (MIA)-induced osteoarthritis rat model was used in the study. Three milligram of MIA was intra-articularly injected into the left knee of SD rat (280-300g) to induce degradation of cartilage (Ponomis et al, Pain; 2005: 339). The rats showing pain-related behaviors measured by *von Frey* filament test were selected for the evaluation of hChonJb#7. At two weeks post MIA administration, various doses of hChonJb#7 were injected into the same knee. The effect on the mechanical allodynia by hChonJb#7 treatment was evaluated by *von Frey* filament test. After completing the filament tests, the knees were harvested for the histological analysis in the cartilage.
Results: The improvement of pain related behavior was dose-dependently observed earliest from 1 week post hChonJb#7 injections. The minimum effective dose was 3 x 10^4 cells of hChonJb#7. The effect was maintained upto 4 week post hChonJb#7 injections. The histological analysis showed that the integrity of cartilage was severely affected by MIA treatment but hChonJb#7 treatment protected the cartilage from MIA-induced damage when compared with the untreated group.
Conclusions: The current study indicated that the chondrocytes expressing TGF-β (hChonJb#7) reduced pain in a rat model which might explain pain reduction in osteoarthritis patients demonstrated during the clinical trials.

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A SELECTIVE CCR2 ANTAGONIST SHOWED MONOCYTES MIGRATION-INDEPENDENT ANALGESIA IN RAT MODELS OF INFLAMMATORY PAIN

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Purpose: The aim of this study is to demonstrate whether the Chemokine C-C motif (CCR2) receptor is involved in inflammatory pain and which mechanisms could describe its physiological contribution in pain pathways.
Methods: Compound A was tested for *in vitro* properties in native cells (rat whole blood assay) and recombinant cells lines (CHO cells expressing rat CCR2). Binding assay was performed in rat CCR2 receptor membrane (RMB) while functional assays were rat whole blood monocytes shape change and calcium mobilization assay in CHO cell line. Selectivity over CCR5 was investigated by binding assay on CHO cells expressing rat CCR5.
To assess the in vivo profile of compound A, adult (200-275 g) male Wistar-Han (Charles River, Germany) rats undergone intraplantar injection of complete Freund's adjuvant (CFA, 25ug/ul by Sigma Aldrich) or intraarticular injection with 1 mg of monosodium iodoacetate (MIA, 50 ul by Sigma Aldrich) for induction of paw inflammatory pain or osteoarthritis (OA), respectively.
Analgesic properties of compound A were assessed by using paw pressure test (Randall Selitto test, UgoBasile, Italy) at 24 hrs post CFA injection and by Incapacitance tester (manufactured by Boehringer-Ingelheim) the weight bearing (WB) deficit was assessed at 3 days post MIA injection. In addition anti-edema properties were investigated in the CFA model measuring changes in the paw volume as assessed by pletysmography (UgoBasile, Italy).
Tissues were collected from injured paws or joints, for further histological examination. All experimental procedures were approved by the ethics committee and the Regierungspräsidium Tübingen (VVH 06-007).
Results: In rat compound A is a selective CCR2 antagonist with Ki in rat RMB of 3.6 nM, with no binding properties to the closest homologous CCR5 (Ki=2920 nM). In addition, it reversed monocytes shape changes (IC50 4.3 nM) and inhibited Calcium mobilization in CHO cells (IC50=1.4 nM) proving to be a full antagonist devoid of any agonistic activity.
In the CFA model, Compound A showed a dose dependent anti-hyperalgesic effect after acute treatment. The highest dose of 10 mg/kg, orally (PO) achieved full effect comparable to celecoxib (30 mg/kg, PO) while the minimal effective dose was measured at 1 mg/kg, PO. Moreover, unlike celecoxib repeated doses of compound A did not prevent edema formation in the CFA model.
In the MIA model compound A, like celecoxib, showed no effect in the WB deficit when dosed acutely, however it significantly reversed pain-like behaviour when given by subchronic treatment. Furthermore histological findings revealed that compound A has no effect in reducing monocytes migration in the CFA paw or MIA joint.
Conclusions: Overall our data support a CCR2 antagonist to have the potential to provide analgesia in nociceptive pain condition. In addition preclinical data suggest that analgesic properties of CCR2 antagonists in pain inflammatory models can not be attributed to blockage of monocytes migration.

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MEASUREMENT OF PAIN IN AN ACUTE MURINE ARTHRITIS PAIN MODEL USING A DYNAMIC WEIGHT BEARING DEVICE AND EVOKED PAIN RESPONSES: EFFECT OF INTRA-ARTICULAR CAPSAICIN PRETREATMENT

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Purpose: Murine models are important to study arthritis pain and new analgesics, but the measurement of pain in mice is challenging. The Dynamic Weight Bearing (DWB) device measures individual limb forces and time spent bearing weight on each limb during spontaneous activity. Evoked pain behaviors in mice are sensitive to change due to arthritis pain and analgesia. We hypothesized that mice with acute arthritis would have measurable changes in DWB due to joint pain that would correlate with evoked pain behaviors and that this could be prevented by pre-treating with intra-articular (IA) capsaicin. We measured DWB and Evoked Pain Scores (EPS) in acute arthritis to determine if DWB correlates with EPS and whether it is a reliable measure of spontaneous pain behavior in animals with arthritis. To test the reliability of DWB in differentiating arthritic from nonarthritic animals, some mice were pretreated with capsaicin to prevent development of arthritis. We also measured substance P in the dorsal root ganglia of animals with and without arthritis and with morphine (MOR) and capsaicin (CAP) treatment.
Methods: C57Bl6 mice were used for all experiments. Acute inflammatory arthritis was produced by IA injection of 10μl 2.5% carrageenan into the left knee 2-4 hours prior to pain behavior testing. Analgesic controls were injected with 2.5% carrageenan diluted in MOR solution